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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 239/91, 215/00, 239/72, A61P 29/00, A61K 31/505, 31/47 | **A3**

(11) International Publication Number: **WO 00/12497**

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/US99/19846

(22) International Filing Date: 27 August 1999 (27.08.99)

(30) Priority Data:
09/141,916 28 August 1998 (28.08.98) US

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(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

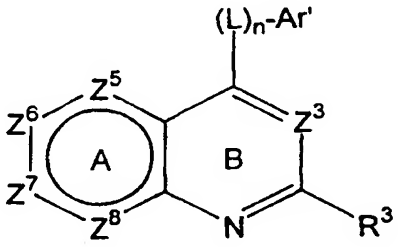
(88)Date of publication of the international search report:
29 June 2000 (29.06.00)

Date of publication of the amended claims:
8 September 2000 (08.09.00)

(54) Title: QUINAZOLINE DERIVATIVES AS MEDICAMENTS

(57) Abstract

The invention is directed to methods to inhibit TGF-β and/or p38-α kinase using compounds of formula (1) or the pharmaceutically acceptable salts thereof wherein R^3 is a noninterfering substituent; each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N; each R^2 is independently a noninterfering substituent; L is a linker; n is 0 or 1; and Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1–3 noninterfering substituents.



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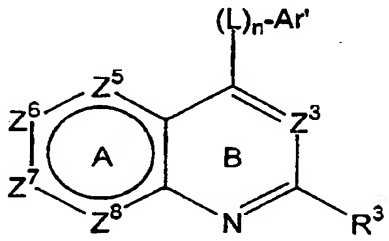
AMENDED CLAIMS

[received by the International Bureau on 19 June 2000 (19.06.00);
original claims 1-22replaced by amended claims 1-20 (6 pages)]

1. A compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 comprises a substituted or unsubstituted aromatic or heteroaromatic moiety;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

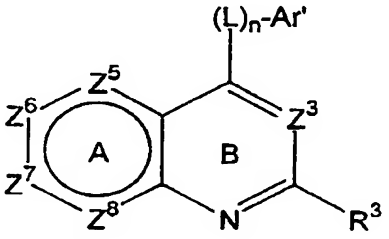
each R^2 is independently a noninterfering substituent;

L is a linker of the formula $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, NR^1, $NR^1CO(CR^2_2)_l$, or $OCO(CR^2_2)_l$, wherein l is 0-3 and m is 0-4, R^1 is H, acyl, alkyl, arylacyl or arylalkyl where the aryl moiety may be substituted or substituted by 1-3 noninterfering groups;

n is 1; and

Ar is a monocyclic or fused aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents, wherein 2 said substituents may form a 5-7 member cyclic, optionally heterocyclic, aliphatic ring.

2. A compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 comprises a substituted or unsubstituted aromatic or heteroaromatic moiety;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

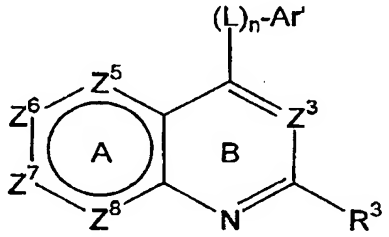
each R^2 is independently a noninterfering substituent;

L is a linker of the formula $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $NR^1(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, or $OCO(CR^2_2)_l$, wherein l is 0-3 and m is 0-4, wherein R^1 is H, acyl, alkyl, arylacyl or arylalkyl where the aryl moiety may be unsubstituted or substituted by 1-3 noninterfering groups;

n is 1; and

Ar is a monocyclic or fused ring aromatic or heteroaromatic system optionally substituted with 1-3 noninterfering substituents.

3. A compound of the formula:



(1)

or the pharmaceutically acceptable salts thereof

wherein R^3 is an unsubstituted or substituted aromatic or heteroaromatic moiety;

each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R^2 is independently a noninterfering substituent;

L is a linker;

n is 0 or 1; and

Ar' is a monocyclic or fused ring aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

4. The compound of claim 1 or 2 wherein R^3 is an aromatic or heteroaromatic moiety which is unsubstituted or substituted with 1-3 substituents.

5. The compound of claim 4 wherein said substituents are independently selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C) and with respect to any aryl or heteroaryl moiety, said group further including alkyl (1-6C).

6. The compound of claim 1, 2 or 3 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

7. The compound of claim 6 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, or morpholinyl, all of which may optionally be substituted.

8. The compound of claim 1, 2 or 3 wherein each R^2 is independently halo or a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N.

9. The compound of claim 8 wherein each R^2 is independently H, alkyl, alkenyl, alkynyl, acyl or hetero-forms thereof or is aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C), or

R^2 is selected from the group consisting of halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, NRSOR, $NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, NRSOR, $NRSO_2R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C).

10. The compound of claim 9 wherein said substituents on R^2 are independently selected from the group consisting of R^4, halo, OR^4, NR^4_2, SR^4, $-OOCR^4$, $-NROCR^4$, $-COOR^4$, R^4CO, $-CONR^4_2$, $-SO_2NR^4_2$, CN, CF_3, and NO_2, wherein each R^4 is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R^4 or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

11. The compound of claim 3 wherein L is $S(CR^2_2)_m$, $-NR^1SO_2(CR^2_2)_l$, $SO_2(CR^2_2)_m$, $SO_2NR^1(CR^2_2)_l$, $NR^1(CR^2_2)_m$, $NR^1CO(CR^2_2)_l$, $O(CR^2_2)_m$, or $OCO(CR^2_2)_l$,

R^1 is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C);

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR_2, SR, -SOR, $-SO_2R$, -OCOR, -NRCOR, $-NRCONR_2$, -NRCOOR, -NRSOR, $-NRSO_2R$, $-OCONR_2$, RCO, -COOR, $-SO_3R$, $-CONR_2$, SO_2NR_2, CN, CF_3, and NO_2, wherein each R is independently H or alkyl (1-4C); and

R^2 is as defined in claim 9.

12. The compound of any of claims 1-3 which is selected from the group consisting of

2-phenyl-4-(4-pyridylamino)-quinazoline;

2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino -6-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and

2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-quinazoline.

13. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity which composition comprises a therapeutically effective amount of a compound of any of claims 1-12 in admixture with at least one pharmaceutically acceptable excipient.

14. The composition of claim 13 which further contains an additional therapeutic agent.

15. The composition of claim 14 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

16. The use of the compound of any of claims 1-12 or a pharmaceutical composition thereof in a method to treat conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity, which method comprises administering to a subject in need of such treatment said compound or composition.

17. The use of claim 16 wherein said condition is a proinflammation response or a fibroproliferative response or both.

18. The use of claim 17 wherein said proinflammation response is multiple sclerosis rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, or pyresis.

19. The use of claim 17 wherein said fibroproliferative response is associated with a renal disorder, a vascular disorder, a fibrosis, an autoimmune disorder, an eye disease, excessive scarring, a neurological condition, myelofibrosis, tissue thickening, nasal polyposis, a polyp, liver cirrhosis, or osteoporosis.

20. The use of claim 19 wherein said renal disorder, is glomerulonephritis, diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in transplant patients receiving cyclosporin, and HIV-associated nephropathy; and

wherein said vascular disorder is progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, eosinophilic fascitis, morphea, or Raynaud's syndrome; and

wherein said fibrosis is associated with adult respiratory distress syndrome, idiopathic pulmonary fibrosis, interstitial pulmonary fibrosis, cardiac fibrosis, keloid formation, or hypertrophic scarring; and

wherein said autoimmune disorder is systemic lupus erythematosus, scleroderma, or rheumatoid arthritis; and

wherein said eye disease is retinal detachment, cataracts, or glaucoma; and

wherein said neurological condition is CNS injury, Alzheimer's disease, or Parkinson's disease.